IAP12 Rec'd PCT/PTO 1 6 APR 2007

PATENT ATTORNEY DOCKET NO. 01948/090003

Certificate of Mailing: Date of Dep	osit: <u>April 10, 2007</u>
I hereby certify under 37 C.F.R. § 1.8(a) that this correspondence as first class mail with sufficient postage on the discommissioner for Patents, P.O. Box 1450, Alexandria, Van	ate indicated above and is addressed to Mail Stop PCT,
Megan Kiley Printed name of person mailing correspondence	Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Neel et al.

Confirmation No.: 2583

Serial No.:

10/520,225

Art Unit:

1618

Filed:

November 10, 2005

Examiner:

Not Yet Assigned

Customer No.:

21559

Title:

COMBINATION OF MTOR INHIBITOR AND A TYROSINE KINASE

INHIBITOR FOR THE TREATMENT OF NEOPLASMS

Mail Stop PCT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants submit the references listed on the enclosed Form PTO-1449, copies of which are enclosed, with the exception of U.S. patents and U.S. patent application publications. A copy of a search report from a corresponding international application is also enclosed.

Submission of this statement is not a representation that a search has been made, nor is the inclusion of information in this statement an admission that the information is material to patentability.

This statement is being filed before the receipt of a first Office action on the merits.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 10, 2007

Paul T! Clark
Reg. No. 30,162

Jeffry J. Elison, Reg. No. 51,649

for Paul T. Clark

Clark & Elbing LLP 101 Federal Street Boston, MA 02110

Telephone: 617-428-0200 Facsimile: 617-428-7045

2

SUBSTITUTE FORM PTO-1449		Attorney Docket No.	01948/090003
(MODIFIED) PATENT AND TRADEMARK OFFICE		Serial No.	10/520,225
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary) (37 C.F.R. § 1.98(b))		Applicant	Neel et al.
		Filing Date	November 10, 2005
		Group	1618
		IDS Filed	April 10, 2007

		U.S.	PATENT DOCUMENTS			
Examiner's Initials	Document Number	Publication Date	Patentee or Applicant	Class	Subclass	Filing Date (If Appropriate)
	5,990,109	Nov. 23, 1999	Chen et al.			
	2004/0167134	Aug. 26, 2004	Bruns et al.			
	2002/0051730	May 2, 2002	Bodnar et al.			
	FOREI	GN PATENT OR P	UBLISHED FOREIGN PATENT	APPLICATI	ON	
Examiner's Initials	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation (Yes/No)
	WO 02/092091	Nov. 21, 2002	WIPO			
	OTHER DOCUM	MENTS (INCLUDIN	IG AUTHOR, TITLE, DATE, PLA	CE OF PU	BLICATION)	
	Atkins et al., "Gleeve Novartis Press Rele		uction Modulators for Cancer Th	nerapy: A Ne	ew Paradigm fo	r Drug Discovery,"
	Blume-Jensen and Hunter, "Oncogenic Kinase Signalling," Nature 411:355-365 (2001).					
	Bridges, "Chemical Inhibitors of Protein Kinases," Chem. Rev. 101:2541-2571 (2001).					
Cortez et al., "The Bcr-Abl Tyrosine Kinase Activates Mitogenic Signaling Pathways and Stimulates G1-to-S phase Transition in Hematopoietic Cells," <i>Oncogene</i> 15:2333-2342 (1997)						
	Dancey and Sausville, "Issues and Progress with Protein Kinase Inhibitors for Cancer Treatment," <i>Nature Reviews</i> 2:296-313 (2003).				Nature Reviews	
	Druker et al., "Inhibition of Bcr-Abl Tyrosine Kinase as a Therapeutic Strategy for CML," Oncogene 21:8541-8546 (2002).				21:8541-8546	
Fukazawa et al., "Mitogen-Activated Protein/Extracellular Signal Regulated Kinase Kinase (MEK) Inhibitors Restore Anoikis Sensitivity in Human Breast Cancer Cell Lines with a Constitutively Activated Extracellular-Regulated Kinase (ERK) Pathway," <i>Mol. Cancer. Ther.</i> 1:303-309 (2002).						
	Gale and Yancopoulos, "Growth Factors Acting via Endothelial Cell-Specific Receptor Tyrosine Kinases: VEGFs, Angiopoietins, and Ephrins in Vascular Development," Genes & Development 13:1055-1066 (1999).			nases: VEGFs, 9).		
	Garber, "Rapamycin Institute 93:1517-15		New Way to Target the Cancer	Cell Cycle,"	Journal of Natio	onal Cancer
	Geoerger et al., "An /Medulloblastoma M	titumor Activity of the	ne Rapamycin Analog CCI-779 i ent and in Combination Chemot	n Human Pr therapy," Ca	imitive Neuroed	ctodermal Tumor 527-1532 (2001).
7	•	****				

EXAMINER	DATE CONSIDERED
	-

EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.

(37 C.F.R. § 1.98(b))		IDS Filed	April 10, 2007
(Ose several sneets if necessary)		Group	1618
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		Filing Date	November 10, 2005
INFORMATION DISCLOSLIDE		Applicant	Neel et al.
(MODIFIED) PATENT AND TRADE	PATENT AND TRADEMARK OFFICE	Serial No.	10/520,225
	U.S. DEPARTMENT OF COMMERCE	Attorney Docket No.	01948/090003

	Gorre et al., "Clinical Resistance to STI-571 Cancer Therapy Caused by BCR-ABL Gene Mutation or Amplification," Science 293:876-880 (2001).
	Grünwald et al., "Inhibitors of mTOR Reverse Doxorubicin Resistance Conferred by PTEN Status in Prostate Cancer Cells," Cancer Res. 62:6141-6145 (2002).
	Guba et al., "Rapamycin Inhibits Primary and Metastatic Tumor Growth by Antiangiogenesis: Involvement of Vascular Endothelial Growth Factor," <i>Nature Medicine</i> 8(2):128-135 (2002).
	Haskell et al., "c-SRC Tyrosine Phosphorylation of Epidermal Growth Factor Receptor, P190 RhoGAP, and Focal Adhesion Kinase Regulates Diverse Cellular Processes," <i>Chem. Rev.</i> 101:2425-2440 (2001).
	Hidalgo and Rowinsky, "The Rapamycin-Sensitive Signal Transduction Pathway as a Target for Cancer Therapy," Oncogene 19:6680-6686 (2000):
	Hilger et al., "The Ras-Raf-MEK-ERK Pathway in the Treatment of Cancer," Onkologie 25:511-518 (2002).
	Hoover et al., "Overcoming STI571 Resistance with the Farnesyl Transferase Inhibitor SCH66336," <i>Blood</i> 100:1068-1071 (2002).
	Humar et al., "Hypoxia Enhances Vascular Cell Proliferation and Angiogenesis In Vitro via Rapamycin (mTOR)-dependent Signaling," <i>The FASEB Journal</i> 16:771-780 (2002).
;	Huse and Kuriyan, "The Conformational Plasticity of Protein Kinases," Cell 109:275-282 (2002).
	Jones and Kazlauskas, "Growth Factor-Dependent Signaling and Cell Cycle Progression," Chem Rev. 101:2413-2423 (2001).
	Konecny and Pegram, "Novel Cancer Therapy: Tyrosine Kinase Inhibitors," Oncology Special Edition 5:67-68 (2002).
	Kurup et al., "Comparative QSAR Study of Tyrosine Kinase Inhibitors," Chem. Rev. 101:2573-2600 (2001).
	Laughner et al., "HER2 (neu) Signaling Increases the Rate of Hypoxia-Inducible Factor 1α (HIF-1α) Synthesis: Novel Mechanism for HIF-1-Mediated Vascular Endothelial Growth Factor Expression," <i>Molecular and Cellular Biology</i> 21(12):3995-4004 (2001).
	Luan et al., "Rapamycin Blocks Tumor Progression: Unlinking Immunosuppression from Antitumor Efficacy," Transplantation 73(10):1565-1572 (2002).
	MacDonald et al., "Clinical Pharmacokinetics and Therapeutic Drug Monitoring of Sirolimus," Clin. Ther. 22 Suppl B. B101-121 (2000).
	Marley et al., "Effects of Combinations of Therapeutic Agents on the Proliferation of Progenitor Cells in Chronic Myeloid Leukaemia," <i>Br. J. Haematol.</i> 116:162-165 (2002).
	"Vascular Endothelial Growth Factor," Mini-Reviews and Technical Information, R&D Systems , www.mdsystems.com
	Morin, "From Oncogene to Drug: Development of Small Molecule Tyrosine Kinase Inhibitors as Anti-tumor and Anti-

EXAMINER	DATE CONSIDERED
EXAMINER: Initial citation considered. Draw line through citation form with the next communication to applicant.	n if not in conformance and not considered. Include copy of this

	SUBSTITUTE FORM PTO-1449		Attorney Docket No.	01948/090003
	(MODIFIED) PATENT AND TRADEMARK OFFICE		Serial No.	10/520,225
	INFORMATIO	ON DISCLOSURE	Applicant	Neel et al.
	INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary) (37 C.F.R. § 1.98(b))		Filing Date	November 10, 2005
			Group	1618
			IDS Filed	April 10, 2007

	angiogenic Agents," Oncogene 19:6574-6583 (2000).
	Nguyen et al., "The Role of Phosphatidylinositol 3-Kinase, Rho Family GTPases, and STAT3 in Ros-induced Cell Transformation," <i>The Journal of Biological Chemistry</i> 977:11107-11115 (2002).
	Podsypanina et al., "An Inhibitor of mTOR Reduces Neoplasia and Normalizes p70/S6 Kinase Activity in Pten* Mice," PNAS USA 98(18):10320-10325 (2001).
	Porosnicu et al., "Co-treatment with As ₂ 0 ₃ Enhances Selective Cytotoxic Effects of STI-571 Against Bcr-Abl-Positive Acute Leukemia Cells," <i>Leukemia</i> 15:772-778 (2001).
	Ravandi et al., "Modulation of Cellular Signaling Pathways: Prospects for Targeted Therapy in Hematological Malignancies," Clinical Cancer Research 9:535-550 (2003).
	Sattler et al., "Critical Role for Gab2 in Transformation by BCR/ABL," Cancer Cell 1:479-492 (2002).
	Sawyers, "Rational Therapeutic Intervention in Cancer: Kinases as Drug Targets," Current Opinion in Genetics & Development, 12:111-115 (2002).
	Schlessinger, "Cell Signaling by Receptor Tyrosine Kinases," Cell 103:211-225 (2000).
	Schmelzle and Hall, "TOR, a Central Controller of Cell Growth," Cell 103:253-262 (2000).
	Sebolt-Leopold, "Development of Anticancer Drugs Targeting the MAP Kinase Pathway, Oncogene 19:6594-6599 (2000).
	Sekulié et al., "A Direct Linkage Between the Phosphoinositide-3-Kinase-AKT Signaling Pathway and the Mammalian Target of Rapamycin in Mitogen-Stimulated and Transformed Cells," <i>Cancer Res.</i> 60:3504-3513 (2000).
	Shah et al., "Multiple Brc-ABL Kinase Domain Mutations Confer Polyclonal Resistance to the Tyrosine Kinase Inhibitor Imatinib (STI571) in Chronic Phase and Blast Crisis Chronic Myeloid Leukemia," <i>Cancer Cell</i> 2:117-125 (2002).
	Shawver et al., "Smart Drugs: Tyrosine Kinase Inhibitors in Cancer Therapy," Cancer Cell 1:117-123 (2002).
	Simon, "Receptor Tyrosine Kinases: Specific Outcomes from General Signals," Cell 103:13-15 (2000).
	Skorski et al., "Phosphatidylinositol-3 Kinase Activity is Regulated by BCR/ABL and is Required for the Growth of Philadelphia Chromosome-Positive Cells," <i>Blood</i> 86(2):726-736 (1995).
	Skorski et al., "Transformation of Hematopoietic Cells by BCR/ABL Requires Activation of a PI-3k/Akt/-Dependent Pathway," <i>EMBO J.</i> 16(20):6151-6161 (1997).
	Thiesing et al., "Efficacy of STI571, an Abl Tyrosine Kinase Inhibitor, in Conjunction With Other Antileukemic Agents Against Bcr-Abl-Positive Cells," <i>Blood</i> 96:3195-3199 (2000).
	Topaly et al., "Synergistic Activity of the New ABL-Specific Tyrosine Kinase Inhibitor STI571 and Chemotherapeutic Drugs on BCR-ABL-Positive Chronic Myelogenous Leukemia Cells," <i>Leukemia</i> 15:342-347 (2001).
-	

EXAMINER	DATE CONSIDERED
EXAMINER: Initial citation considered. Draw line through citation form with the next communication to applicant.	n if not in conformance and not considered. Include copy of this

SUBSTITUTE FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE	Attorney Docket No.	01948/090003	
(MODIFIED) PATENT AND TRADEMARK OFFICE		Serial No.	10/520,225
INFORMATIO	ON DISOLOGUES	Applicant	Neel et al.
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary) (37 C.F.R. § 1.98(b))		Filing Date	November 10, 2005
		Group	1618
		IDS Filed	April 10, 2007

Traxler et al., "Tyrosine Kinase Inhibitors: from Rational Design to Clinical Trials," <i>Medicinal Research Reviews</i> 21:499-512 (2001).
Yu et al., "Pharmacologic Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase/Mitogen-activated Protein Kinase Inhibitors Interact Synergistically with STI571 to Induce Apoptosis in Bcr/Abl-expressing Human Leukemia Cells," Cancer Research 62:188-199 (2002).
Zamore et al., "RNAi: Double-Stranded RNA Directs the ATP-Dependent Cleavage of mRNA at 21 to 23 Nucleotide Intervals," Cell 101:25-33 (2000).
International Search Report for PCT/US2003/20972, mailed March 22, 2004.